REMARKS

Initially, Applicants wish to thank the Examiner for the careful consideration given this case. Claims 1 and 3-8 and 10-20 are currently pending in this case. Claims 9, 21 and 22 are hereby cancelled without prejudice to presentation in this or related cases. Newly-introduced Claims 23 and 24 are based upon the Examiner's suggestion on Page 4 of the present Office Action, as further explained below. It is hereby asserted that no new matter has been introduced through any amended or newly introduced claims.

This response addresses those issues raised in Office Action of April 14, 2004. In light of the amendments and comments presented herein, it is believed that all pending claims are allowable, and timely notice to such effect is respectfully requested.

Objections

The Examiner objects to Claim 14 because of the misspelling of diphtheria. Applicants' Agent thanks the Examiner for noticing this error. Claim 14 has been amended to reflect the Examiner's comments. Reconsideration and withdrawal of the objection is respectfully requested.

35 U.S.C. §112 rejections

The Examiner rejects Claims 1 and 3-20 under 35 U.S.C. § 112, ¶2 as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner objects to the language "purified peptide fragment" found in Claim 1 and rejects Claim 1 under 35 U.S.C. §112, ¶2 as being indefinite. To avoid any confusion on this point, Claim 1 has been amended to recite "purified peptide" rather than "purified peptide fragment." It is respectfully submitted that this amendment resolves any uncertainty to the

meaning of Claim 1. Reconsideration and withdrawal of this rejection is respectfully requested. In addition, it is submitted that Claims 3-6 were rejected under §112, ¶2 because of the rejection of Claim 1. These claims have also been amended to remove the term "fragment". Reconsideration and withdrawal of the rejections of these claims are also respectfully requested.

The Examiner rejects Claim 7 regarding the language "group consisting essentially of" under 35 U.S.C. §112, ¶2 as being indefinite. While the Applicants do not agree with the Examiner on this point, to promote prosecution of the present invention Claim 7 has been amended to read "group consisting of" to address Examiner's concern. Given that Claim 7 was not rejected in view of any prior art, it is submitted that Claim 7 is presently allowable and notice to that effect is respectfully requested. In addition, it is assumed that Claims 9, 15, and 18-20 are rejected under §112, ¶2 because of the rejection of Claim 7. Claim 9 has been cancelled. Reconsideration and withdrawal of the rejection of Claims 15 and 18-20 are also respectfully requested.

The Examiner rejects Claims 8 and 10 under 35 U.S.C. § 112, ¶2 as being indefinite in that Claim 8 does not recite any structural alteration of the recited peptides in Claim 7 that would further Claim 7. In order to address the Examiner's concern, Claims 8 and 10 have been amended to remove the language "capable of being." Claim 9 has therefore been cancelled as being duplicative of Claim 8 as amended. It is respectfully submitted that this amendment addresses the concerns of the Examiner. Reconsideration and withdrawal of this rejection are respectfully requested. In addition, it is assumed that Claims 11-14 and 16-17 are rejected under §112, ¶2 because of the rejection of Claims 8 and 10. Reconsideration and withdrawal of the rejection of these claims are also respectfully requested.

The Examiner rejects Claims 1 and 3-6 as failing to comply with the written description requirement of 35 U.S.C. § 112, ¶1. As the Examiner notes, Claim 1 is drawn to a purified peptide with selective binding to tumor derived endothelial cells, wherein the peptide

possesses a charge motif of positive-positive-neutral hydrophobic, wherein the peptide is not greater than fifty amino acid residues in length. On page 3 of the present Office Action, the Examiner states that:

> Numerous functional attributes are also tolerated in members of the genus because the limitation "binding to tumor derived endothelial cells" reads on binding to any subcomponent of tumor derived endothelial cells, such as those taught by Epstein et al (WO 90/03801) to be fibronectin, laminin and type IV collagen (page 14, lines 18-24), as well as binding to any antigen which is selectively expressed in the vicinity of a tumor such as cell adhesion molecules responsible for adherence of PMN leukocytes, fibrin, fibrin degradation productions and fibronectin (page 14, line 32 to page 15, line 3), the receptors flk and kdr, and heparin-containing proteoglycans as taught by Senger et al (US 6,022,541, column 6, lines 48-52), as well as the TIE2/Tek as taught by the abstract of Peters et al (British Journal of Cancer, 1998, Vol. 77, pp. 51-56). (Emphasis added.)

Applicants wish to point out that the emphasized portion of the quote above was incomplete. The claim reads "A purified peptide with selective binding to tumor-derived endothelial cells..." The present Claim 1 (and Claims 3-6 which depend therefrom) specifically recites peptides that bind selectively to tumor derived endothelial cells. Moreover, the present patent application teaches a manner by which a particular peptide may be tested to determine if it specifically binds to tumor derived endothelial cells. Within the context of the present claims, it is not enough for a peptide to bind to endothelial cells non-specifically. Claim 1 very explicitly requires peptides having selective binding to tumor derived endothelial cells.

The references that the Examiner has cited in this passage are inapplicable in light of the claimed invention. For example, fibronectin is well known to be involved with eukaryotic cell-to-cell interactions during wound healing, not just in tumor derived endothelial cells. Similarly, laminin is a common extracellular matrix protein and does not specifically bind to tumor derived endothelial cells. Furthermore, flk and kdr receptors and TIE2/Tek are endothelial specific with no suggestion present in the cited references that they specifically bind to tumor derived endothelial cells. In addition, none of these peptides satisfy the claim limitation of being less than 50 amino acids. In contrast to the Examiner's assertion that these peptides read onto

the pending claims, the pending claims do not encompass these species and these references are not relevant to the pending claims.

The Examiner further asserts on Page 4 of the present Office Action that SEQ ID NOS: 1-5 do not adequately describe the claimed genus, because the genus includes peptides which bind to numerous sub-endothelial components and antigens which are selectively accessible on, or selectively expressed by, tumor associated endothelium. It is unclear to Applicants to which peptides the Examiner is referring. Indeed, all of the examples cited by the Examiner in that paragraph of the present Office Action are inapplicable to the claimed invention.

Claims 1 and 3-6 satisfy the written description requirement of §112, ¶1 as interpreted by the USPTO. The Written Description Guidelines (Guidelines for Examination of Patent Applications under the 35 U.S.C. § 112, ¶1, "Written Description" Requirement, Fed. Reg. 66(4): 1099-1111) state that:

> The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, *i.e.* **structure** or other physical and/or chemical properties, by **functional characteristics** coupled with a known or disclosed correlation between function and structure, **or by a combination of such identifying characteristics**, sufficient to show the application was in possession of the claimed genus." *Written Description Guidelines* at 1106 (Internal citations omitted. Emphasis added.)

The presently-rejected claims disclose structural (less than 50 amino acids, having a charge motif of positive-positive-neutral hydrophobic) as well as functional (selective binding to tumor derived endothelial cells) characteristics, clearly in accord with this passage from the Written Description Requirements. Reconsideration and withdrawal of the rejection under §112, ¶1 are respectfully requested.

35 U.S.C. §§ 102 and 103 rejections

The Examiner rejects Claims 1 and 3-5 under 35 U.S.C. 102(a) as being anticipated by Smith et al. (WO 00/04052). As the Examiner notes, Smith et al. disclose anti-angiogenic agents linked to a peptidic membrane binding entity. The anti-angiogenic peptides of Smith et al. are not shown to be specific to tumor derived endothelial cells, but only to new blood vessels. While the growth of tumors often involves the growth of new blood vessels, the presently-claimed peptides of the present invention bind specifically to tumor derived endothelial cells. While Smith et al. discuss their invention in terms of the effects on tumor endothelium, there is nothing in Smith et al. that demonstrates that these peptides bind specifically to tumor derived endothelial cells. A claim is anticipated by a prior art reference if, and only if, each and every claim limitation may be found, either expressly or inherently described, in a single prior art reference. MPEP § 2131.01. It is respectfully submitted that Smith et al. does not satisfy this requirement. Accordingly, the rejection of Claims 1 and 3-6 under § 102 is inappropriate. Reconsideration and withdrawal of this rejection are respectfully requested.

The Examiner rejects Claims 1 and 3-6 under 35 U.S.C. § 103(a) as being unpatentable over Smith et al. (WO 00/04052) in view of Epstein et al. (WO 90/03801). The Examiner notes that Epstein et al. teach a delivery vehicle having the ability to concentrate at the site of neoplastic tissue wherein said delivery vehicle is conjugated to a tumor imaging agent. Epstein et al. discloses delivery vehicles having specificity for sub-endothelial components of the blood vessel wall that become accessible in structurally abnormal endothelium. However, the delivery vehicles of Epstein et al. are based upon metabolic effects, namely increasing blood flow to tumors and allowing antibody-based molecules to accumulate at that location (*See, e.g.*, Abstract), not by specific binding to tumor endothelial cells.

Furthermore, the immuno-proteins disclosed by Epstein et al. are much larger than the 50 amino acids required by the present claims. Given these two attributes of Epstein et

al.'s peptides, there is no reason for one of ordinary skill in the art to employ Epstein et al. in generating small peptides of less than 50 amino acids. Reconsideration and withdrawal of the present rejection are respectfully requested.

Claims 1 and 4 are rejected under 35 U.S.C. § 102(a) as being anticipated by Oku et al. (WO 00/23476). Oku et al. state that the peptides described in that invention are specific to neovasculature. These peptides would, thus, likely bind to any neovasculature including that in healing wounds, retinopathy, and inflammation. Thus, there is no indication that these peptides would specifically bind to tumor-derived endothelial cells. A claim is anticipated by a prior art reference if, and only if, each and every claim limitation may be found, either expressly or inherently described, in a single prior art reference. MPEP § 2131.01. It is respectfully submitted that Smith et al. does not satisfy this requirement. Accordingly, the rejection of Claims 1 and 3-6 under § 102 is inappropriate. Reconsideration and withdrawal of this rejection are respectfully requested.

Claims 1 and 3-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Epstein et al. (cited above) in view of Oku et al. (cited above). As noted above, Epstein et al. does not teach, alone or in combination with Oku et al. each and every claim limitation found in Claim 1, namely specific binding to tumor derived endothelial cells. To establish a *prima facie* case of obviousness of a claimed invention, all of the claim limitations must be taught or suggested in the cited references. MPEP § 2143.01. It is submitted that the cited references do not satisfy this requirement in the claims as presently amended. Reconsideration and withdrawal of this rejection are respectfully requested.

New Claims 23 and 24

Following the suggestion by the Examiner on Page 4 of the present Office Action, Applicants have introduced new Claims 23 and 24. Applicants submit that Claims 23 and 24 are fully supported by the present specification.

By the enclosed amendments and remarks, Applicant has fully addressed all of the issues raised by the Examiner in the Office Action mailed on April 24, 2004. In view of the amendments and remarks included herein, it is respectfully submitted that the present application is in condition for final allowance and notice to such effect is respectfully requested. If the Examiner believes that additional issues need to be resolved before this application can be passed to issue, the undersigned invites the Examiner to contact him at the telephone number provided below.

Respectfully submitted,

Dated: August 10, 2004

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